## REMARKS

Applicants file the following remarks for entry of record.

Favorable reconsideration is requested.

Claims 18, 20-23, 26, 27, 29, 30, and 34-42 are pending.

The Official Action of January 9, 2012 finally rejected these claims under 35 U.S.C. §103.

The rejection is premised on the combination of Bargiotti et al. (U.S. 5,304,687) in view of: Kuhl et al. (Cancer Chemother. Pharmacol., 1993, 33, 10-16), Nakamura et al. (Gan. To Kagaku Ryoho 1988, Aug 15 (8 Pt2), 2562-7, English Abstract), Gorbunova (Intrahepatic Arterial Infusion…Liver, 1990), and Brem et al. (U.S. 5,626,862).

For this rejection to be *prima facie* tenable under §103 there must be an objectively reasonable expectation of success, see e.g., MPEP 2143.02 and the cases therein including e.g. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The claims are to a method of treating human liver cancer. The active is MMDX. None of the applied references show MMDX for liver cancer. Bargiotti et al. purports to disclose MMDX and human mammary carcinoma. Kuhl et al. mention MMDX and human leukemia. The other references do not disclose MMDX.

The rejection avers that using MMDX for liver cancer would have been obvious, and expectedly successful, because MMDX is "activated in the liver to a metabolite which cross links to DNA and is 10 times more potent." The Official Action cites Kuhl et al. in this regard.

The supposition that MMDX would be potentiated in the liver and, therefore, would have been thought effective for treating liver cancer is fatally flawed for the following reason. It presupposes a healthy liver. The claims, on the other hand, are directed to treating

liver cancer. One in the art would have appreciated that the liver metabolism, relied upon by the Official Action, would therefore be compromised. The organ that, in other cancer circumstances, may potentiate MMDX, is the very organ now under attack. It is self-evident that a cancerous liver is not a healthy liver and *ipso facto* does not function as one.

At the time of filing, the artisan knew *inter alia* that the liver microsome P-450 was the microsome principally involved in drug metabolism. The artisan also knew, however, that when the liver itself was under siege with cancer, this microsome, as well as other such components, was adversely affected. See e.g. Hamamoto et al. "Microsomal Cyctochrome P-450-linked Monooxygenase Systems and Lipid Composition of Human Hepatocelluar Carcinoma" *British Journal of Cancer*, 59(1) pp. 6-11 (1989), the abstract of which clearly teaches:

> "In microsomes of hepatocelluar carcinoma tissues, there was as much cyctochrome P-450 and other redox components as in the normal liver tissues, but cytochrome P-450 in liver cancer tissues was unstable and easily converted to cytochrome P-420. The specific activities of NADPH- and NADH-ferricyanide and cytochrome c reductase of each sample were also measured. In the microsomes of the cancer tissues, the specific activities were remarkably reduced compared with those of normal liver tissues."

The artisan also knew that cytochrome P-420, into which P-450 is "easily converted" in cancerous liver tissue, is an inactive form, see e.g. Omura et al. "The Carbon Monooxide-binding Pigment of Liver Microsomes" *Journal of Biological Chemistry*, vol. 34, No.7, July 1964, pp. 2370-2378.

See also Eriksson et al. "Distinctive Biochemical Pattern Associated with Resistance of Hepatocytes in Hepatocyte Nodules during Liver Carcinogenesis" *Environmental Health Perspectives*, Vol. 49, pp. 171-174 (1983); and El Mouelhi et al. "Hepatic Drug-metabolizing enzymes in Primary and Secondary Tumors of Human Liver" *Cancer Research*,

47, pp. 460-466 (1987) which indicate that drug-metabolizing liver enzymes are markedly decreased in cancerous livers.

The aforementioned references are at Exhibit A.

Case law requires that for the prior art to render a claimed invention obvious

> "there must have been, at the time the invention was made, a reasonable expectation of success in applying [the prior art] teachings."

*Life Technologies Inc. v. Clontech*, 56 USPQ2d 1186, 1190 (Fed. Cir. 2000).

If the prior art indicates uncertainty, then a conclusion of non-obviousness prevails. *Eli Lilly and Co. v. Teva Pharmaceuticals*, 96 USPQ2d 1375 (Fed. Cir. 2010) is in point. There, claims to the treatment of osteoporosis using a known compound (raloxifene) were in play. The prior art taught poor bioavailability for that compound in other conditions. In finding the claims patentable, the Federal Circuit approvingly noted the District Court finding

> "that the widely reported bioavailability concerns would have precluded a person of ordinary skill in the art from reasonably expecting to successfully treat postmenopausal osteoporosis with raloxifene."

56 USPQ2d at 1381.

And further found there was;

> "no evidence from before the time of invention that would teach, suggest, or motivate or supply any common sense reason for a person of ordinary skill in the art to reject the bioavailability concerns…"

56 USPQ2d at 1382.

Here, it was known that MMDX was potentiated by the liver. The Official Action relies upon this potentiation to envision a reasonable expectation of success in using MMDX to treat liver cancer. But it was also known that when the liver itself was cancerous —which is the

subject matter of the instant claims— the responsible microsomes were severely depleted and/or converted to inactive forms. The basis on which the official expectation of success stands thus falls away, and the rejection collapses.

Similar to *Eli Lilly*, the reported concerns over microsomal diminishment and alteration in cancerous livers necessarily precludes one in the art from having a reasonable expectation of potentiation and of successfully treating that same liver cancer with MMDX.

None of the applied references, alone or in combination, usurp or change this known detrimental microsomal aspect of liver cancer and the lack of expectation generated thereby.

Moreover, with this as the state of the art, the fact that MMDX is effective at all, and more saliently, at the low dosages claimed, is entirely unexpected, non-obvious, and patentable.

Applicants respectfully request reconsideration and withdrawal of the rejection.

WHEREFORE, it is believed the instant case is in condition for allowance, passage to which is earnestly solicited.

Respectfully submitted,

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